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Prevention of chronic kidney disease: A global challenge

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Prevention of chronic kidney disease: A global challenge. In view of the increasing number of patients requiring renal replacement therapy (RRT) every year worldwide, attention has focused over the last two decades on meeting the health care need of patients with end-stage renal failure (ESRF). More recently, increasing awareness of the growing burden of chronic kidney disease (CKD), with a large percentage of the population affected by early stages of CKD, has shifted attention and health care priority to the prevention and early detection of CKD. This article addresses issues related to general population as well as targeted screening, favoring the latter. It also examines some of the screening initiatives undertaken in both the developing and developed worlds. It also highlights the links between albuminuria, CKD, and cardiovascular disease (CVD) as an increasing number of studies identify albuminuria/proteinuria, as well as CKD as major markers of CVD. Finally, a brief review is included of primary and secondary intervention strategies for CKD and issues related to their implementation: manpower and funding.

CHRONIC KIDNEY DISEASE: THE GLOBAL CHALLENGE

Chronic kidney disease (CKD) is emerging in the 21st century as a global public health issue. Currently, more than 1 million patients with end-stage renal failure (ESRF) are on renal replacement therapy (RRT) worldwide [1], with as many as 2 million predicted to require therapy by 2010 [1, 2]. The majority of these patients come from developed nations that can afford the cost of RRT [3], whereas a large number of those requiring treatment in developing countries do not have access to RRT. The cost of RRT is prohibitive for many economies and countries, because there is a clear and direct relationship between gross national product and availability of RRT [3, 4]. It is therefore imperative to shift the emphasis of the global approach to CKD toward early detection and prevention because management of the growing number of patents with ESRF may be beyond even the most affluent of countries. Within the next 10 years, it is estimated that the annual cost of ESRF management in the United States will rise to approximately US $30 billion, consuming a considerable part of the health care budget.

Key words: albuminuria, microalbuminuria, proteinuria, screening, CKD.

Patients with ESRF are likely to represent the tip of the iceberg of the entire burden of CKD [5]; it has been estimated that the number of patients with earlier stages of CKD (stages 1 to 4) are likely to exceed by as much as 50-fold that of those reaching ESRF (stage 5). The Third National Health and Nutrition Examination Survey (NHANES III) has estimated that 11% (19 million) of the adult American population has some degree of renal involvement [6]; approximately 11 million individuals have stages 1 and 2 CKD with glomerular filtration rate (GFR) exceeding 60 mL/min [6], with another 8 million with moderate (stage 3) and severe (stage 4) renal insufficiency. By contrast, only 300,000 have reached stage 5 (ESRF). Early detection of CKD and interventions aimed at preventing its progression into more advanced stages are likely to be key factors in alleviating the future burden of ESRF.

It is increasingly recognized that the burden of CKD is not limited to its impact on demands for RRT but has major impacts on overall population health. It is now well established that the prognosis and, in particular, the cardiovascular morbidity and mortality, of patients with diabetes mellitus and those with systemic hypertension depend on renal involvement [7]. Therefore, CKD, through its impact on cardiovascular risk in these patients, impacts directly on the global burden of death due to cardiovascular diseases [7]. Consequently, early detection and prevention of progressive CKD may not only alleviate the future burden of ESRF but also reduce the cardiovascular morbidity and mortality associated with highly prevalent conditions such as diabetes and hypertension.

CKD DETECTION AND PREVENTION PROGRAMS

In recent years, a number of screening strategies have been implemented for the detection of CKD. Some have focused on the entire population, whereas others targeted a specific group(s) within the population. General population screening approaches have been undertaken in the United States (NHANES III) [6], Australia [Australian Diabetes, Obesity and Lifestyle study (AusDiab Study)] [8], Japan (Okinawa Screening Program) [9], The Netherlands [Prevention of Renal and Vascular End-stage

Disease (PREVEND) Study] [10], Iceland [11], as well as India [12] and Singapore [13].

NHANES III was carried out in the United States from 1988 to 1994. It involved 15,626 participants and determined the prevalence of various stages of CKD in the United States adult population using spot urine albumin and calibrated serum creatinine levels [6]. It reported that the overall prevalence of CKD among the population was 11% (19 million United States adults). It pointed to a large number (around 6%) of cases of asymptomatic CKD in the presumably normal general population.

The AusDiab Study was a population-based, cross-sectional survey to determine the prevalence of diabetes mellitus, obesity, cardiovascular risk factors, and indicators of kidney disease in Australian adults [8]. A representative sample of the Australian adult population comprising 11,247 participants was studied from May 1999 to December 2000 and showed that 3% of the population had proteinuria, whereas 11% were found to have significant renal impairment (GFR <60 mL/min).

In Japan, the Okinawa screening program carried out between 1983 and 1984 investigated more than 106,000 individuals followed-up for 17 years [9]. The study identified initial obesity, dyslipidemia, and smoking as significant risk factors for the subsequent development of albuminuria. It also identified proteinuria [9] and obesity [14] as major risk factors for the development of CKD.

In Europe, the PREVEND study undertaken in the Dutch city of Groningen evaluated almost half the population (approximately 40,000 individuals) in a cross-sectional cohort study [10]. The main objective of PREVEND was to assess the prevalence of microalbuminuria in the general population; the study found that around 7% of those screened had albuminuria. Individuals with the highest level of albuminuria were found to have, over a 3-year follow-up period, the highest incidence of cardiovascular death [10]. This observation highlighted the likely association between albuminuria and endothelial dysfunction, and atherosclerosis and cardiovascular morbidity and mortality.

A study in Iceland evaluated 18,912 patients aged 33 to 81 years and found the prevalence of CKD (raised serum creatinine) very low (0.22%) [11]. This study may have underestimated the true prevalence of early CKD because testing that relies on serum creatinine alone is likely to fail to detect a large number of patients with CKD and GFRs above 30 mL/min.

The National Kidney Foundation of Singapore set up a comprehensive program for CKD prevention in 2000 and is currently evaluating in excess of 450,000 Singaporeans [13]. The program detected significant urinary abnormalities (ranging from 5% to 8% proteinuria and/or hematuria) among the general population and high-risk individuals with a family history of renal insufficiency [13].

In India, the Chennai community-screening program screened around 25,000 individuals and found approximately 6% with previously undiagnosed hypertension and 4% with diabetes mellitus [12]. Subsequently, management of identified patients with hypertension and diabetes with readily available and cheap drugs achieved target values in the majority of patients [12].

Specific population-targeted approaches have investigated ethnic minorities, such as the Australian Aborigines [15] and the Zuni Indians in the Southwest United States [16]. Australian Aborigines of the Tiwi Islands have a high death rate attributable to ESRF [15]. The annual incidence of ESRF (2760 per million) in Tiwi Islanders is among the highest in the world (15 times that of the general Australian population). This may explain the very high (5-fold that of the general population) incidence of cardiovascular mortality on this island. The Tiwi screening program revealed an overall prevalence of albuminuria of 55% and, when followed longitudinally, it highlighted all future risks for renal deaths and cardiovascular morbidity and mortality. Of note, intervention in this high-risk group with angiotensin-converting enzyme (ACE) inhibition reduced blood pressure, proteinuria, and overall mortality [15].

The Zuni Kidney Project targeted Zuni Indians in the United States, where most of the population is affected by CKD due to glomerulonephritis and diabetic nephropathy, and 2% have ESRF (a staggering prevalence rate of 17,400 per million population) [16]. The Zuni Kidney Project showed a prevalence of albuminuria ranging from 12% to 36% among the general population [16].

The National Kidney Foundation of the United States piloted from 1997 to 1999 the Kidney Early Evaluation Program (KEEP) to identify individuals at risk of CKD and the prevalence of CKD among those at risk (patients with diabetes, patients with hypertension, as well as first-degree relatives of patients with CKD) [17]. By the end of 2003, KEEP had recruited over 22,000 participants and revealed an overall prevalence of the different stages of CKD in about 50% of those studied. Of these, 26% had albuminuria, around 16% had been found with elevated serum creatinine levels, and others (3%) had asymptomatic urinary abnormalities [17].

Different communities probably will have to adopt different methods that best suit their environment, taking into consideration such factors as health awareness and availability of human and material resources. Targeted population screening will suit well-developed health systems with accurate records and databases. Whole population surveys will increase health awareness in countries with less-sophisticated health systems and help detect a significant proportion of underdiagnosed individuals with hypertension and diabetes [12]. It may also have the added advantage, as shown in the Chennai Project in Southern India [12], of improving the

quality of care of those with diabetes and hypertension, thus hopefully minimizing their renal and cardiovascular complications.

CKD AND CARDIOVASCULAR DISEASE: COMMON RISK FACTORS

The aforementioned screening programs often relied on urinary albumin measurement to identify individuals at risk of developing CKD. The prevalence of albuminuria in previously healthy individuals varied from 2.4% to 3% in the AusDiab study [8], 6.3% in NHANES III [6], and 7% in PREVEND [10]. Higher prevalence was reported in targeted screening programs; Zuni Kidney Project: 12% to 36% [16] and KEEP: (26%) [17]. It remains uncertain as to what proportion of patients with albuminuria will go on to develop CKD with renal insufficiency.

Beyond its potential for predicting the development of CKD, albuminuria may also be of value in identifying patients at risk of cardiovascular disease (CVD). Microalbuminuria is associated with a higher (6- to 8-fold increase) cardiovascular morbidity and mortality in patients with diabetes [7, 18, 19]. It has been suggested that the overall mortality of some groups of patients with diabetes is comparable with that of the general population in the absence of renal involvement. Microalbuminuria is also a predictor of increased mortality in the elderly [20]. In essential hypertension [21], as in CKD [22], the rate of decline in renal function is proportional to the severity of albuminuria/proteinuria.

Testing for microalbuminuria in the absence of associated risks such as hypertension, diabetes, or old age has received less attention. The PREVEND study group, using the albumin concentration of a spot morning urine sample, noted that urinary albumin excretion is associated with renal functional abnormalities in a nondiabetic or hypertensive population [23]. The study also observed a link between microalbuminuria and cardiovascular as well as all-cause mortality in the general population [19, 23].

A growing body of evidence suggests that conventional risk factors for CVD are also associated with increased risk of CKD [24]. The Framingham Offspring Study investigated predictors of new onset CKD in 2585 healthy participants who attended a baseline examination from 1978 to 1982 and a follow-up examination from 1998 to 2001 [25]. Two hundred forty-four (9.4%) of those studied developed CKD. Identifiable risk factors were increasing age [odds ratio (OR) = 2.36 per 10-year increment], increased body mass index (OR = 2.60), diabetes (OR = 2.38), smoking (OR = 1.42), and hypertension (OR = 1.57). Those with impaired kidney function at the onset also were at higher risk.

The Okinawa study of over 100,000 individuals identified obesity, smoking, and hypertriglyceridemia as predictors of albuminuria over a 10-year observation period [9]. Proteinuria [26] as well as obesity [14] also predicted the development of ESRF.

The Multiple Risk Factors Intervention Trial (MRFIT) of over 300,000 male United States citizens made similar observations, identifying hypertension, obesity, and hyperlipidemia as risk factors for the development of CKD [27].

The Washington County survey in Maryland, United States, of 23,534 men and women over a 20-year period identified baseline blood pressure, cigarette smoking (hazard ratio: 2.4 in men and 2.9 in women), and treated diabetes (hazard ratio: mean: 5 and women: 10.7) as risk factors for the development of CKD [28].

Undoubtedly, common risk factors appear to predispose to both renal and cardiovascular diseases in developed countries. Early detection and prevention may have an impact on the outcome of both renal and cardiovascular morbidity and mortality. These may also be of relevance to the increasingly westernized societies of the emerging world. Westernized and urbanized societies in emerging countries may be acquiring a similar risk profile to that of the developed world, with diabetes and hypertension leading the risk factors for CKD.

Also, developing countries continue to suffer from the massive burden of infectious diseases and infestations with their associated renal involvement. The global burden of human immunodeficiency virus, with 40 million infected individuals [29], hepatitis C virus (170 million) [30], malaria (300 million cases per year) [31], schistosomiasis (200 million) [32], as well as tuberculosis (200 million) [33], is compounded by the high incidence of CKD in affected individuals. This, in turn, increases the morbidity and mortality associated with these infections worldwide. Detection and prevention of CKD programs in the emerging world have to take the infectious disease burden in mind.

CKD: SCREENING APPROACHES

Pitfalls of measurement of albuminuria/proteinuria

Many of the above-mentioned studies have relied on measurement of urinary albumin or protein for the detection of patients at risk for CKD. Some have questioned the value of mass population screening for proteinuria, reasoning that its yield of treatable diseases, especially in young adults, is too low to be justifiable [34]. Orthostatic proteinuria, diet, menstruation, transient fever, hydration status, and physical activity are all factors that may affect the level of proteinuria and undermine the outcome of an untargeted randomly selected mass proteinuria screening exercise. The assessment of proteinuria as a marker of

CKD can be limited by the potential for misclassification of individuals because of variability of protein levels in the individual's urine over time and the extent to which conditions at that time may obscure the true level. Of note, in the NHANES III survey, only 63% of the initial positive results of microalbuminuria could be confirmed on repeat testing [6], thus indicating that one spot test may overestimate the prevalence of albuminuria. Variability of urine albumin excretion rates with age was also demonstrated in NHANES III, with abnormal albuminuria rates varying from 7% in the group that was 20 to 39 years of age to about 30% in the group that was more than 70 years of age in the general population [35].

Furthermore, besides diabetic nephropathy, little is known of the renal outcome of patients with isolated microalbuminuria. The Nord-Trondelag Health Study in Norway (HUNT) demonstrated that 3 positive urine samples for elevated albumin/creatinine ratio were superior to a fewer number of samples in predicting proteinuria [36]. A timed 24-hour urine albumin excretion rate, considered the most accurate method of albuminuria estimation, reasonably eliminates the variability of urinary albumin concentration due to activity and posture. However, such approach is limited because it is an arduous task for the patient and there are inaccuracies in the urine collection. The Nord-Trondelag Health Study (HUNT) group concluded that in a randomly selected apparently healthy population, as a result of low-positive predictive value and reduced reliability, microalbuminuria did not satisfy the criteria for a good screening test [37].

Therefore, it has been suggested that rather than screening for albuminuria alone, albuminuria and hematuria should be tested for in combination, and may be more powerful in predicting renal parenchymal damage than proteinuria alone [38].

The KEEP study group's set objective of targeting the population with known risk factors for kidney disease by screening with the aim of maximizing yield is a pragmatic approach to the issue of population screening [17]. The effectiveness of targeted screening was shown by comparing the results of KEEP (elevated serum creatinine: 5.4%) with those of other similar studies for the same United States population (NHANES III: 3%).

In Western nations, where diabetes and hypertension account for more than 50% of cases of ESRD, care of patients will increasingly depend on primary care physicians. Consequently, there is a need for clear and unambiguous guidelines that can be applied universally. It has been argued that emphasis on the prevention of ESRD should be directed toward such high-risk groups for maximum yields, and that screenings should be carried out at regular intervals. On the other hand, mass population screening may be less cost effective [17].

The strategic approach to screening in developing countries requires special attention. Lifestyle changes that affect the developing world will have a major impact on cardiovascular as well as renal morbidity and mortality rates in years to come. Population education initiatives and programs aimed at early detection of diabetes and hypertension and their management are warranted and will have to engage health care agencies and organizations. They will also require the full commitment of governments and their agencies in those countries.

CKD DETECTION AND PREVENTION PROGRAMS: A GLOBAL APPROACH

Lifestyle modification

In addressing challenges posed by the worldwide CKD pandemic, diet and lifestyle modifications, and the tight control of diabetes and hypertension are imperative, stressing patency policies that keep highly effective drugs out patients' reach, should be given greater consideration and urgency.

Increasing evidence suggests that lifestyle modifications such as weight reduction, exercise, and dietary manipulations can be effective and protective. A number of trials have shown that lifestyle modifications (weight reduction with or without regular exercise) can considerably reduce the incidence of type 2 diabetes in overweight individuals with impaired glucose tolerance [39, 40]. Dietary approaches to reduce blood pressure consisting of dietary salt restrictions as well as diets rich in fruit and vegetables and low in saturated fat have proved effective. This was examined in the Dietary Approaches to Stop Hypertension-Sodium Trial [41, 42]. Undoubtedly, improved population health with reduction of excessive weight, regular exercise, and dietary approaches will lead to a reduction in the growing number of patients with diabetes and hypertension in the long run. This is likely to have a major impact on the incidence of CKD and associated CVD.

Smoking has been implicated in the onset of microalbuminuria in individuals with and without diabetes [43]. Cessation of smoking will undoubtedly be beneficial in individuals at risk of renal disease as well as CVD. Alcohol has been linked with the development of ESRF, and it may also increase cardiovascular risks through hemodynamic effects on systemic blood pressure [44].

Pharmacologic approaches

Control of hypertension is the single most important intervention to reduce both albuminuria/proteinuria and subsequent development of CKD in patients with and without diabetes alike [45]. It is therefore imperative to detect prehypertensive states, aim at lower blood pressure levels in the general population, and be even

more aggressive with lowering blood pressure in patients with hypertension and underlying CKD [46]. It has been suggested that every elevation of systolic blood pressure above 115 mm Hg in the general population is associated with a doubling of the risk of CVD. In patients with CKD, target blood pressure levels should be less than 130/80 mm Hg in the absence of diabetes or proteinuria and <125/75 mm Hg in patients with diabetes and those with proteinuria in excess of 1 g/24 h [46].

The control of glycemia has been shown to be a major factor in the prevention and progression of diabetic nephropathy [47–49]. Target glycosylated hemoglobin levels around 7% have been recommended. Realistically, levels consistently less than 8% should be protective without exposing patients to the risks of hypoglycemic complications.

Control of albuminuria/proteinuria is also an important factor in slowing the progression of diabetic and nondiabetic CKD [50, 51]. For that reason, antihypertensive approaches using ACE inhibitors or angiotensin receptor blockers have been widely advocated [52]. Their impact on renal function is often proportional to their proteinuria-lowering effect. Inhibition of the renin-angiotensin-aldosterone system may also have additional renoprotective effects through inhibition of renal inflammation and fibrosis. Furthermore, these agents are also known to be cardioprotective and may therefore minimize cardiovascular complications of CKD.

Dyslipidemia has been implicated in progression of CKD. Subsequently, lipid reduction with HMG CoA reductase inhibitors (statins) has been shown to be protective in experimental CKD and may have additive effects when combined with inhibitors of the rennin-angiotensin-aldosterone system [53]. A systematic review of lipid-lowering trials in CKD suggested a potential benefit in slowing the rate of progression of chronic kidney failure [54]. The cardioprotective potential of statins is now well established.

In light of the above, the concept of multiple drug therapy has been put forward after a meta-analysis of over 750 trials involving around 400,000 participants suggested that up to 80% reduction in CVD events can be obtained by a combination treatment of a polypill containing an ACE inhibitor, a statin, and other cardioprotective agents such as aspirin and vitamins [55]. A similar therapeutic approach may be adoptable in the future in selected patients with progressive CKD in an attempt to prevent the development of progressive renal insufficiency and associated cardiovascular complications. This may be a pragmatic and cost-effective approach to reduce the global burden of renal and CVD. For that well-defined population, screening programs have to be initiated to identify at-risk individuals, along with the application of the aforementioned early and systematic preventive treatment approaches.

MANPOWER TO IMPLEMENT CKD PREVENTION AND PREVENTION PROGRAMS

Detection and prevention of CKD programs require considerable resources both in terms of manpower and funds. Availability of such resources will depend primarily on the leadership of nephrologists worldwide. It will also depend on the training and availability of a new generation of dedicated nephrologists with an interest and training in epidemiology and public health issues. For that, nephrology training programs will have to be tailored in the future to the requirements of the community in which the nephrologist will practice. The Sheffield Kidney Institute in the UK has a longstanding track record in training nephrologists from developing countries. Recent emphasis has shifted to acquiring more epidemiology, biostatistics, and public health knowledge. Nephrologists have also been encouraged to acquire the necessary skills to set up relevant databases and registries. The European Kidney Institute was founded in 2004 and brings together the expertise of nephrologists from the Mario Negri Insitute (Bergamo, Italy), the Groningen Research Institute for Kidney Disease (Groningen, The Netherlands), and the Sheffield Kidney Institute (Sheffield, United Kingdom) to provide a European-training infrastructure capable of supporting detection and prevention projects worldwide.

Nephrologists will have to rely on well-trained and motivated community health workers. Such a multidisciplinary approach has proved effective and successful when applied in projects such as that of the Chennai Community Screening project in India [12] or of the Tiwi Islanders in Australia [15]. In both, nephrology leadership, along with a dedicated community health care force, proved a powerful and successful combination.

FUNDING OF CKD DETECTION AND PREVENTION PROGRAMS

Funding of detection and prevention of CKD programs will have to engage governments, nongovernmental and charitable organizations, as well as the pharmaceutical industry. Commitment of local governmental agencies at regional and national levels is a prerequirement to the implementation of many such initiatives. Nongovernmental and charitable organizations have an important role to play in lobbying and encouraging governments to take up and support such programs. Finally, the pharmaceutical industry will have to face up to its responsibilities in supporting such detection of CKD programs, knowing that many patients identified will undoubtedly require their products to prevent progression of underlying kidney diseases [56].

CONCLUSION

A multifaceted approach is urgently needed to stem the global tide of ESRF. This calls for concerted efforts from governmental agencies, international bodies, and organizations, including the pharmaceutical industry. It calls for a rethinking of medical and nephrologic training and that of associated health workers to meet community-based demands. Ultimately, population-increased education and awareness will contribute to its well-being.

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